Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-16. (canceled)

17.(currently amended) A method of screening an individual for predisposition for ~~detecting a variant gene having a polymorphism associated with~~ reduced metabolism of ~~a substrate selected from the group consisting of~~ a CYP3A4 substrate, or a CYP3A5 substrate ~~and a GSTM1 substrate in an individual~~, said method comprising:

~~(a) obtaining a nucleic acid sample comprising a gene isolated from said individual, said gene selected from the group consisting of a CYP3A4 gene, a CYP3A5 gene and a GSTM1 gene; and,~~

~~(b) detecting~~ determining the presence or absence in the individual of one or both of ~~in said individual of a polymorphism selected from the group consisting of~~

~~(i) a substitution of~~ a G ~~nucleotide for an A nucleotide~~ at position -392 of the promoter of ~~said~~ a CYP3A4 gene with respect to the start codon of said CYP3A4 gene~~, wherein the presence of said substitution is associated with reduced CYP3A4 substrate metabolism;~~; and

~~(ii) a substitution of~~ a G ~~nucleotide for an A nucleotide~~ at a position ~~-147 of the promoter of said CYP3A5 gene~~corresponding to nucleotide 1037 in SEQ ID NO:4~~, wherein the presence of said substitution is associated with reduced CYP3A5 substrate metabolism:~~; and

~~(iii) a GSTM1 null mutation, wherein the presence of said GSTM1 null mutation is associated with reduced GSTM1 substrate metabolism.~~

identifying the individual as having a predisposition for reduced metabolism of the CYP3A4 substrate or the CYP3A5 substrate if one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene and the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4 are determined to be present in the individual.

18.(currently amended) The method of Claim 17, wherein said ~~method further~~ determining comprises, ~~for an individual having one of said nucleic acid sequences,~~ determining whether said individual is homozygous or heterozygous for ~~the polymorphism.~~one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene and the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4.

19.-21. (canceled)

22.(currently amended) The method of Claim 17, wherein ~~said gene is a CYP3A4 gene and wherein said~~ the CYP3A4 substrate is ~~selected from the group consisting of cyclophosphamide and BCNU~~a nitrogen mustard or BCNU and the CYP3A5 substrate is a nitrogen mustard or BCNU.

23.-24. (canceled)

25.(currently amended) A method for selecting a treatment for a cancer patient, said method comprising:

~~obtaining a nucleic acid sample comprising a gene isolated from said individual, said gene selected from the group consisting of a CYP3A4 gene, a CYP3A5 gene and a GSTM1 gene;~~

~~detecting~~ determining the presence or absence in the cancer patient of one or more of ~~in said individual of apolymorphism selected from the group consisting of~~

~~(i) a substitution of~~ a G ~~nucleotide for an A nucleotide~~ at position -392 of the promoter of ~~said~~ a CYP3A4 gene with respect to the start codon of ~~said~~ the CYP3A4 gene~~, wherein the presence of said substitution is associated with reduced CYP3A4 substrate metabolism;~~;

~~(ii) a substitution of~~ a G ~~nucleotide for an A nucleotide~~ at a position ~~-147 of the promoter of said CYP3A5 gene~~ corresponding to nucleotide 1037 in SEQ ID NO:4~~, wherein the presence of said substitution is associated with reduced CYP3A5 substrate metabolism;~~; and

~~(iii)~~ a GSTM1 null mutation~~, wherein the presence of said GSTM1 null mutation is associated with reduced GSTM1 substrate metabolism~~; and

~~selecting a cancer treatment~~

selecting a treatment selected from the group consisting of:~~regime that does not include administration of an anti-cancer agent selected from the group consisting of cyclophosphamide and BCNU if one or more of said polymorphisms are present~~

a treatment that does not comprise administration of an anti-cancer prodrug metabolized to the active drug by CYP3A4 or CYP3A5 if one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4, is determined to be present in the cancer patient;

a treatment that comprises administration of an anti-cancer prodrug metabolized to the active drug by CYP3A4 or CYP3A5 if one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4, is determined to be absent in the cancer patient;

a treatment that does not comprise administration of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be absent in the cancer patient;

a treatment that comprises administration of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be present in the cancer patient;

a treatment that comprises administration of a higher than conventional dose of an anti-cancer prodrug metabolized to the active drug by CYP3A4 or CYP3A5 if one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4, is determined to be present in the cancer patient;

a treatment that comprises administration of a conventional dose of an anti-cancer prodrug metabolized to the active drug by CYP3A4 or CYP3A5 if one or both of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene or the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4, is determined to be absent in the cancer patient;

a treatment that comprises administration of a higher than conventional dose of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be absent in the cancer patient; and

a treatment that comprises administration of a conventional dose of an anticancer drug which is an alkylating agent metabolized by GSTM1 if the GSTM1 null mutation is determined to be present in the cancer patient.

26.(currently amended) The method of Claim 25, wherein said ~~method further~~ determining comprises, ~~for an individual having one of said polymorphisms,~~ determining whether ~~said individual~~the cancer patient is homozygous or heterozygous for ~~the polymorphism~~ one or more of the G at position -392 of the promoter of the CYP3A4 gene with respect to the start codon of the CYP3A4 gene, the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4, and the GSTM1 null mutation.

27.-29. (canceled)

30.-34. (canceled)

35. (new) The method of claim 17, wherein the determining comprises
obtaining a genomic DNA sample from the individual; and
performing a PCR amplification reaction on the sample using one or both of PCR primer pairs (a) SEQ ID NO:17 and SEQ ID NO:18 or (b) SEQ ID NO:21 and SEQ ID NO:22.

36. (new) The method of claim 22, wherein the CYP3A4 substrate is the nitrogen mustard and the CYP3A5 substrate is the nitrogen mustard.

37. (new) The method of claim 36, wherein the nitrogen mustard is cyclophosphamide.

38. (new) The method of claim 22, wherein the CYP3A4 substrate is BCNU and the CYP3A5 substrate is BCNU.

39. (new) The method of 25, wherein the anti-cancer prodrug is a nitrogen mustard.

40. (new) The method of 39, wherein the nitrogen mustard is cyclophosphamide.

41. (new) The method of 25, wherein the alkylating agent is a nitrosourea, a nitrogen mustard or cisplatin.

42. (new) The method of 41, wherein the nitrosourea is BCNU.

43. (new) The method of claim 25, wherein the determining comprises

obtaining a genomic DNA sample from the cancer patient; and

performing a PCR amplification reaction on the sample using one or more of PCR primer pairs: (a) SEQ ID NO:17 and SEQ ID NO:18; (b) SEQ ID NO:21 and SEQ ID NO:22; or (c) SEQ ID NO:23 and SEQ ID NO:24.

44. (new) The method of claim 25, the method comprising determining the presence or absence in the cancer patient of each of

the G at position -392 of the promoter of a CYP3A4 gene with respect to the start codon of the CYP3A4 gene;

the G at a position corresponding to nucleotide 1037 in SEQ ID NO:4; and

the GSTM1 null mutation